MEGESTROL ACETATE - megestrol acetate tablet
BARR LABORATORIES, INC.

Revised APRIL 2001
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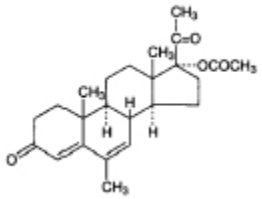
Rx only

DESCRIPTION

Megestrol acetate tablets, USP is a synthetic, antineoplastic and progestational drug. Megestrol acetate is a white, crystalline solid chemically designated as 17 α-acetyloxy-6-methylpregna-4,6-diene-3,20-dione. Solubility at 37°C in water is 2 mcg per mL, solubility in plasma is 24 mcg per mL. The structural formula is represented as follows:



$C_{24}H_{32}O_4$ Molecular Weight: 384.51

Megestrol acetate is supplied as tablets for oral administration containing 20 mg or 40 mg megestrol acetate.
Inactive Ingredients: Anhydrous lactose, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.

CLINICAL PHARMACOLOGY

While the precise mechanism by which megestrol produces its antineoplastic effects against endometrial carcinoma is unknown at the present time, inhibition of pituitary gonadotropin production and resultant decrease in estrogen secretions may be factors. There is evidence to suggest a local effect as a result of the marked changes brought about by the direct instillation of progestational agents into the endometrial cavity. The antineoplastic action of megestrol acetate on carcinoma of the breast is effected by modifying the action of other steroid hormones and by exerting a direct cytotoxic effect on tumor cells. In metastatic cancer, hormone receptors may be present in some tissues but not others. The receptor mechanism is a cyclic process whereby estrogen produced by the ovaries enters the target cell, forms a complex with cytoplasmic receptor and is transported into the cell nucleus. There it induces gene transcription and leads to the alteration of normal cell functions. Pharmacologic doses of megestrol acetate not only decrease the number of hormone-dependent human breast cancer cells but also are capable of modifying and abolishing the stimulatory effects of estrogen on these cells. It has been suggested that progestins may inhibit in one of two ways: by interfering with either the stability, availability, or turnover of the estrogen receptor complex in its interaction with genes or in conjunction with the progestin receptor complex, by interacting directly with the genome to turn off specific estrogen-responsive genes.
There are several analytical methods used to estimate megestrol acetate plasma levels, including mass fragmentography, gas chromatography (GC), high pressure liquid chromatography (HPLC) and radioimmunoassay. The plasma levels by HPLC assay or radioimmunoassay methods are about one-sixth those obtained by the GC method. The plasma levels are dependent not only on the method used, but also on intestinal and hepatic inactivation of the drug, which may be affected by factors such as intestinal tract motility, intestinal bacteria, antibiotics administered, body weight, diet, and liver function.
Metabolites account for only 5% to 8% of the administered dose and are considered negligible. The major route of drug elimination in humans is the urine. When radio-labeled megestrol acetate was administered to humans in doses of 4 to 90 mg, the urinary excretion within 10 days ranged from 56.5% to 78.4% (mean 66.4%) and fecal excretion ranged from 7.7% to 30.3% (mean 19.8%). The total recovered radioactivity varied between 83.1% and 94.7% (mean 86.2%). Respiratory excretion as labeled carbon dioxide and fat storage may have accounted for at least part of the radioactivity not found in the urine and feces.
In normal male volunteers (n=23) who received 160 mg of megestrol acetate given as a 40 mg qid regimen, the oral absorption of megestrol acetate appeared to be variable. Plasma levels were assayed by high pressure liquid chromatography (HPLC) procedure. Peak drug levels for the first 40 mg dose ranged from 10 to 56 ng/mL (mean 27.6 ng/mL) and the times to peak concentrations ranged from 1.0 to 3.0 hours (mean 2.2 hours). Plasma elimination half-life ranged from 13.0 to 104.9 hours (mean 34.2 hours). The steady state plasma concentrations for a 40 mg qid regimen have not been established.

INDICATION AND USAGE

Megestrol acetate tablets are indicated for the palliative treatment of advanced carcinoma of the breast or endometrium (i.e., recurrent, inoperable, or metastatic disease). It should not be used in lieu of currently accepted procedures such as surgery, radiation, or chemotherapy.

CONTRAINDICATIONS
History of hypersensitivity to megestrol acetate or any component of the formulation.

WARNINGS
Megestrol acetate may cause fetal harm when administered to a pregnant woman. Fertility and reproduction studies with high doses of megestrol acetate have shown a reversible feminizing effect on some male rat fetuses. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.
The use of megestrol acetate in other types of neoplastic disease is not recommended. (See also **PRECAUTIONS - Carcinogenesis, Mutagenesis, Impairment of Fertility** section.)
Although the glucocorticoid activity of megestrol acetate tablets has not been fully evaluated, evidence of adrenal suppression has been observed. Clinical cases of new onset diabetes, exacerbation of pre-existing diabetes, and Cushing's syndrome have been reported in association with the use of megestrol acetate. Cases of clinically apparent adrenal insufficiency have also been reported in association with megestrol acetate. The possibility of adrenal suppression should be considered in any patient taking or withdrawing from chronic megestrol therapy who presents with symptoms of adrenal insufficiency such as hypotension, nausea, vomiting, dizziness, or weakness. Laboratory evaluation for adrenal insufficiency and replacement stress doses of a rapidly acting glucocorticoid may be indicated for such patients.
Failure to recognize inhibition of the hypothalamic-pituitary-adrenal axis may result in death.

PRECAUTIONS

General
Close surveillance is indicated for any patient treated for recurrent or metastatic cancer. Use with caution in patients with a history of thromboembolic disease.

Use in Diabetics
Exacerbation of pre-existing diabetes with increased insulin requirements has been reported in association with the use of megestrol acetate.

Information for the Patients
Patients using megestrol acetate should receive the following instructions:
1. This medication is to be used as directed by the physician.

2. Report any adverse reaction experiences while taking this medication.

Laboratory Tests
Breast malignancies in which estrogen and/or progesterone receptors are positive are more likely to respond to megestrol acetate.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Administration of megestrol acetate to female dogs for up to 7 years is associated with an increased incidence of both benign and malignant tumors of the breast. Comparable studies in rats and studies in monkeys are not associated with an increased incidence of tumors. The relationship of the dog tumors to humans is unknown but should be considered in assessing the benefit-to-risk ratio when prescribing megestrol acetate and in surveillance of patients on therapy (see **WARNINGS** section).

Pregnancy
Pregnancy Category D: (See **WARNINGS** section.)

Nursing Mothers
Because of the potential for adverse effects on the newborn, nursing should be discontinued if megestrol is required for treatment of cancer.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Weight Gain
Weight gain is a frequent side effect of megestrol. This gain has been associated with increased appetite and is not necessarily associated with fluid retention.

Thromboembolic Phenomena
Thromboembolic phenomena including thrombophlebitis and pulmonary embolism (in some cases fatal) have been reported.

Glucocorticoid Effects
(see **WARNINGS** section.)

Other Adverse Reactions
Heart failure, nausea and vomiting, edema, breakthrough menstrual bleeding, dyspnea, tumor flare (with or without hypercalcemia), hyperglycemia, glucose intolerance, alopecia, hypertension, carpal tunnel syndrome, mood changes, hot flashes, malaise, asthenia, lethargy, sweating and rash.

OVERDOSAGE
No serious unexpected side effects have resulted from studies involving megestrol acetate administered in dosages as high as 1600 mg/day. Oral administration of large, single doses of megestrol acetate (5 g/kg) did not produce toxic effects in mice. Megestrol acetate has not been tested for dialyzability; however, due to its low solubility it is postulated that this would not be an effective means of treating overdose.

DOSAGE AND ADMINISTRATION

Breast Cancer
160 mg/day (40 mg q.i.d).

Endometrial Carcinoma
40 to 320 mg/day in divided doses.
At least 2 months of continuous treatment is considered an adequate period for determining the efficacy of megestrol acetate tablets, USP.

HOW SUPPLIED
Megestrol Acetate Tablets, USP are available as:

20 mg:	White, round, flat-faced, bevel-edged, scored tablet. Debossed with 555/606 on one side and stylized **b** on the other side. Available in bottles of: 100 NDC 0555-0606-02 250 NDC 0555-0606-03 500 NDC 0555-0606-04
40 mg:	White, round, flat-faced, bevel-edged, scored tablet. Debossed with 555/607 on one side and stylized **b** on the other side. Available in bottles of: 100 NDC 0555-0607-02 250 NDC 0555-0607-03 500 NDC 0555-0607-04

Dispense with a child-resistant closure in a well-closed container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).

SPECIAL HANDLING

Health Hazard Data
There is no threshold limit value established by OSHA, NIOSH, or ACGIH.
Exposure or “overdose” at levels approaching recommended dosing levels could result in side effects described above (See **WARNINGS** and **ADVERSE REACTIONS** sections). Women at risk of pregnancy should avoid such exposure.

MANUFACTURED BY
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